UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/242,977	02/26/1999	JAMES M. WILSON	GNVPN.019BUS	1765

25226 7590 07/22/2002

MORRISON & FOERSTER LLP
755 PAGE MILL RD
PALO ALTO, CA 94304-1018

EXAMINER
SHUKLA, RAM R

ART UNIT	PAPER NUMBER
1632	26

DATE MAILED: 07/22/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/242,977	Applicant(s) WILSON ET AL.	
	Examiner Ram Shukla	Art Unit 1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 May 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *19-24,26-28 and 30-35* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *19-24,26-28 and 30-35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 22 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *detailed action* .

DETAILED ACTION

1. Amendments filed 5-7-02 has been received.

2. Claim 18 has been canceled.

3. Amendments to claims 19, 21-24 and 26-28 have been entered.

4. The numbering of claims is not in accordance with 37 CFR 1.126 which requires the original numbering of the claims to be preserved throughout the prosecution. When claims are canceled, the remaining claims must not be renumbered. When new claims are presented, they must be numbered consecutively beginning with the number next following the highest numbered claims previously presented (whether entered or not).

Newly presented misnumbered claims 29-34 have been renumbered 30-35 and entered.Claims 19-24, 26-28 and 30-35 are pending and are instantly under consideration.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claim 19-24, 26-28 remain rejected and claims 30-35 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for reasons of record set forth in the previous office action of 11-23-01.

Applicants have amended claims 21 and 26 by introducing the embodiment "wherein the recombinant AAV is at least as free of the contaminating adenoviral helper virus as is obtained by subjecting said recombinant AAV to four rounds of cesium chloride gradient centrifugation" which would encompass "equal to" or

"more" pure recombinant AAV composition compared to the preparation of recombinant AAV obtained after four rounds of cesium chloride centrifugation. However, the specification does not provide written support either for the phrase it self or for equal to or more pure AAV preparation compared to that obtained by four rounds of cesium chloride centrifugation. It is noted that Applicants did not provide any guidance as to where in the specification the explicit or implicit support for the phrase was provided. It is reiterated that the specification only discloses that the composition was subjected to four rounds of cesium chloride gradient centrifugation and there is no written support in the specification as what would be the contaminating levels of adenoviral helper virus after four rounds of cesium chloride centrifugation and therefore, an artisan would not know what contamination level would be considered to be "at least as free of the contaminating adenoviral helper virus".

When an amendment is filed in reply to an objection or rejection based on 35 U.S.C.112, first paragraph, a study of the entire application is often necessary to determine whether or not "new matter" is involved. Applicant should therefore specifically point out the support for any amendments made to the disclosure. See MPEP 2163.06

8. Claims 19-24 and 26-28 remain rejected and claims 30-35 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a composition comprising a recombinant adeno-associated virus (rAAV suspended in a biological compatible carrier, wherein the rAAV comprises (i) a 5' AAV inverted terminal repeat (ITR), (ii) a nucleic acid sequence encoding human apolipoprotein E (human ApoE) operably linked to a eukaryotic promoter, and (iii) a 3' AAV ITR, and wherein the level of contaminating adenoviral helper virus is same as that obtained by subjecting said recombinant AAV to four rounds of cesium chloride centrifugation and a method of delivering ApoE to a mammal with atherosclerosis, wherein said method comprises the step of administering to the mammal intramuscularly the composition comprising the rAAV and wherein the

ApoE encoding sequence in the composition is expressed in the mammal and wherein a cytotoxic immune response directed against rAAV-transduced cells of the mammal expressing ApoE is absent in the mammal, does not reasonably provide enablement for any and all rAAV vectors wherein the ApoE encoding sequences are not linked to a promoter or wherein multiple ITRs or multiple ApoE encoding sequences are present or wherein the contaminating levels of adenoviral helper virus are lower than the levels of contaminating adenoviral helper virus after subjecting the rAAV to four rounds of cesium chloride centrifugation or wherein the vector is administrated by any method, for reasons of record set forth in the previous office action of 11-23-01. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Response to Arguments

Applicant's arguments filed 5-7-02 have been fully considered but they are not persuasive. Applicants' amendment regarding operable linkage of the ApoE encoding sequences to regulatory sequences is acknowledged and the rejection regarding this issue is withdrawn. Applicants have argued that claims do not recite multiple ITRs, however, this argument is not persuasive because claims do recite 5' ITRs and 3' ITRs which suggests that there could be multiple 5' ITRs or 3' ITRs (see for example claim 21(a)). It is noted that except for a statement that applicants are not required to provide a specific working example for each embodiment encompassed by a claim, applicants did not address any of the scientific issues discussed in the previous office action. Accordingly, the rejection is maintained for reasons of record set forth in the previous office action of 11-23-01

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 19-24, 26-28, and claims 30-35 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 21 and 26 and new claims 31, 34 and 35 are vague and indefinite because the metes and bounds of the claimed invention is not clearly defined as set forth in the previous office action of 11-23-01. It is noted that the amendment to claims 21 and 26 have used a different phrase, however, the specification does not disclose what would be considered the contaminating levels of adenoviral helper virus in the recited recombinant AAV composition that is purified by four rounds of cesium chloride gradient centrifugation. Therefore the metes and bounds of the claimed invention is not clear. It is noted that except for a statement that the amendment renders the rejection moot, applicants did not provide any evidence as to how the rejection is rendered moot.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

11. The obviousness-type double patenting rejection of claims 19-24 and 26-28, set forth in the previous office action of 6-21-00 over claims 1-4 of US Patent 5,866,552 is maintained and newly presented claims 30-35 are rejected for reasons of record set forth in the office action of 6-21-00 and 11-23-01. It is noted that due to an inadvertent error US Patent No was misspelled as 5,866,522 in the

previous office action. Applicants' request that this rejection be deferred until allowance is acknowledged.

12. Claims 19-24 and 26-28 remain provisionally rejected and claims 30-35 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 7-11 of co-pending Application No. 09/757,673 for reasons of record set forth in the office action of 11-23-01. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are directed to a method for expressing a transgene (ApoE in the instant application) in an animal or in a cell or in a patient by introducing a composition comprising an adeno-associated viral vector comprising a transgene (ApoE encoding transgene in the instant application) into the cell such that the transgene is expressed in the cell, wherein the adeno-associated viral vector is free of helper adenovirus contamination. It is noted that although the claims of the instant application recite characteristic of the adeno-associated viral composition as prepared by four rounds of cesium chloride centrifugation, this limitation would still encompass a composition free of helper adenovirus vector because both the applications disclose four rounds of cesium chloride gradient centrifugation for the adeno-associated virus composition. As such, the claims of the co-pending application 09/757,673 make obvious the instantly claimed method and AAV vectors comprising the ApoE gene.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Applicants' request that this rejection be deferred until allowance is acknowledged.

13. Claims 19-24 and 26-28 remain provisionally rejected and claims 30-35 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-6, 9, 20, 21, 23, 25, 26, and 27 of co-pending Application No. 09/237,064 for reasons of record set forth in the office action of 11-23-01. Although the conflicting claims are not identical, they are

not patentably distinct from each other because both sets of claims are directed to a method for expressing a ApoE in an animal/patient by introducing a composition comprising an adeno-associated viral vector comprising ApoE transgene into the cell such that the transgene is expressed in the cell, wherein the adeno-associated viral vector is free of helper adenovirus contamination. It is noted that although the claims of the instant application recite characteristic of the adeno-associated viral composition as prepared by cesium chloride centrifugation, this limitation would still encompass a composition free of helper adenovirus vector. As such, the claims of the co-pending application 09/237,064 make obvious the instantly claimed method and AAV vectors comprising the ApoE gene.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Applicants' request that this rejection be deferred until allowance is acknowledged.

Claim Rejections - 35 USC § 103

14. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

15. Claims 19-24 and 26-28 remain rejected and claims 30-35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Podsakoff et al (US 5,858,351, 1-12-1999, filing date 1-18-1996) in view of Kashyap et al. (Ref CV of Paper No. 11) for reasons of record set forth in the previous office action of 11-23-01.

Response to Arguments

Applicant's arguments filed 5-7-02 have been fully considered but they are not persuasive. Applicants have argued that using same rejection against method of

delivery claims and steps recited therein as against composition claims is improper. However, these arguments are not persuasive because the methods of Podsakoff et al are for treatment of a disease and therefore the rejection is proper. Additionally, the rejection is a 103 rejection not a 102 rejection and the teachings of Podsakoff et al has to be considered in its entirety. Applicants further argue that combination fails to teach delivery by any other route other than intravenous. In response applicants are directed to Podsakoff et al which teaches intramuscular delivery (see col 19 continued in col 20). Next, applicants argue that neither of the documents recognize the problem of immune response associated with helper virus contaminations in AAV preparations. Again, applicants are advised to look at Podsakoff which realizes the problem (see column 1, lines 50-54). It is noted that applicants have emphasized four rounds of purification as the centerpiece of their invention, however, they provide no evidence as to how to differentiate the impurities of an AAV preparation purified by one or two rounds versus four rounds of purification. It is reiterated that the specification does not provide any disclosure as to what level of impurity was present in their preparation. Next, applicants argue that the step of monitoring the mammal for expression of ApoE distinguishes the issues. However, the argument is not persuasive because the step of monitoring the expression is not the novelty of the method and it would be obvious to an artisan to monitor the expression for determining the efficacy of the method. Finally, regarding applicants arguments that absent motivation to deliver ApoE via AAV and a reasonable expectation of success, there can not be a motivation to make the composition whose only purpose would be for in vivo delivery. In response, it is reiterated that Podsakoff teaches AAV for gene delivery and for treating a disease by gene delivery and applicants have not provided any evidence as to why an artisan would not have had reasonable success in making an AAV vector expressing ApoE and use it for treating atherosclerosis.

In conclusion, it is reiterated that at the time of the invention, it would have been obvious to one of ordinary skill in the art to modify the rAAV vector of Podsakoff et al by cloning the ApoE cDNA taught by Kashyap et al e al, produce composition of the virus, purify it be cesium chloride centrifugation and use the

resultant composition for delivery of ApoE gene to animals with reasonable expectation of success because all the pertinent methods are taught by Podsakoff et al and the cDNA for ApoE is taught by Kashyap et al. An artisan would have been motivated to use rAAV based method for ApoE gene delivery to treat atherosclerosis because Podsakoff et all teach that rAAV vector method is unique because of its ability to transduce non-proliferating cells along with the attributes of being inherently defective and nonpathogenic and because it is art recognized that adenovirus mediated gene delivery causes immune response (see lines 50-67 in column 1 of Podsakoff et al).

16. No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

When amending claims, applicants are advised to submit a clean version of each amended claim (without underlining and bracketing) according to **§** 1.121(c). For instructions, Applicants are referred to http://www.uspto.gov/web/offices/dcom/olia/aipa/index.htm.

Applicants are also requested to submit a copy of all the pending/under consideration claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ram R. Shukla whose telephone number is (703) 305-1677. The examiner can normally be reached on Monday through Friday from 7:30 am to 4:00 p.m. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached on (703) 305-4051. The fax phone number for this Group is (703) 308-4242. Any inquiry of a general nature, formal matters or relating to the status of this application or proceeding should be directed to the Dianiece Jacobs whose telephone number is (703) 305-3388.

Ram R. Shukla, Ph.D.

RAM R. SHUKLA, PH.D
PATENT EXAMINER